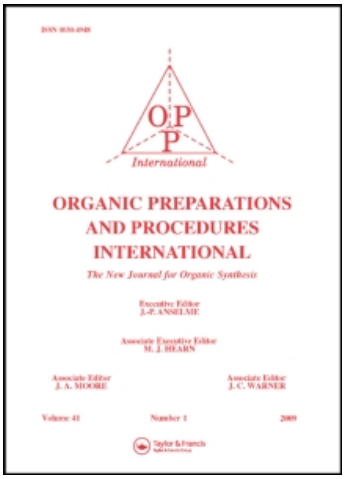

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THE SYNTHESIS OF PHENOLIC ANTIOXIDANTS. 3,5-BIS(3,5-DI-TERT-BUTYL-4-HYDROXYBENZYL)-2,3,6-TRIMETHYLBENZYL DERIVATIVES

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THE SYNTHESIS OF PHENOLIC ANTIOXIDANTS. 3,5-BIS(3,5-DI-TERT-BUTYL-4-HYDROXYBENZYL)-2,3,6-TRIMETHYLBENZYL DERIVATIVES

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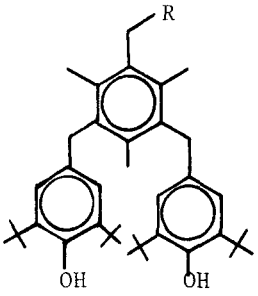
Phenolic and sulfur containing antioxidants have been found to inhibit chemically induced neoplasia in the lung, the forestomach and other target organs of laboratory animals.[1] The phenolic antioxidants that are effective as inhibitors include hydroxyanisole (HA), butylated hydroxyanisole (BHA) and butylated hydroxytoluene.[2-5]. Two of the sulfur containing inhibitors are bis-ethyl xanthogen and disulfiram.[6-8] In our continued search for more potent inhibitors with low toxicity, we have



I

a) R = Cl

b) R = O—⟨⟩—OTHP

c) R = O—⟨⟩(CH3)—OTHP

d) R = O—⟨⟩(CH3)—OTHP

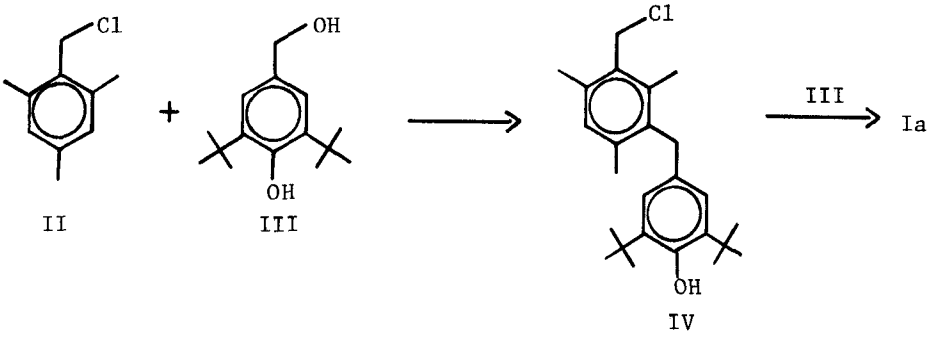
e) R = S–C(=S)–N(Et)$_2$ f) R = S–C(=S)–OEt g) R = O—⟨⟩—OH

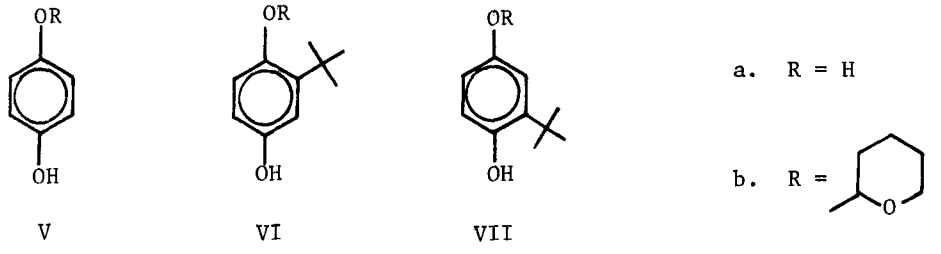
h) R = O—⟨⟩(CH3)—OH i) R = O—⟨⟩(CH3)—OH

directed our effort towards the synthesis of compounds that contain moieties of known inhibitors attached to a bulky backbone.[9] The function of the bulky backbone is to limit absorption from the gastrointestinal tract and thus reduce the toxicity of these potential inhibitors. The integrity of the inhibitor moiety will be preserved as the compounds pass through the digestive tract unchanged.

The bulky backbone chosen for this series of compounds is the 3,5-bis(3,5-di-t-butyl-4-hydroxybenzyl)-2,4,6-trimethylbenzyl group (I). Five compounds (Ie-i), each containing the antioxidant moieties diethyl dithiocarbamate, ethyl xanthogen, HA, 2-BHA, 3-BHA respectively, have been synthesized according to the general synthesis of ether (or thioether).

The precursor Ia, was synthesized in two steps by the sulfuric acid-catalyzed reaction of α-chlorodurene (II) with 2,6-di-t-butyl-4-hydroxymethylphenol (III), in dichloromethane to afford IV which was subsequently alkylated with III in a second step.[10]





In order to prevent disubstitution at both hydroxy groups, Va, VIa and VIIa were converted to the tetrahydropyranyl ethers (Vb-VIIb). Monomesylhydroquinone was synthesized according to the method of Helferich.[11] The free hydroxy group was protected as the THP ether and the mesyl group removed by sodium ethoxide to give Vb. Compound VIb was synthesized by formation of the THP ether of the pivaloyl ester of t-butyl hydroquinone and subsequent removal of the ester group.[12] Compound VIIb was obtained by reaction of VIIa with dihydropyran in dilute solution. The desired product was isolated from the other THP ethers by preparative HPLC.

The sodium salt of ethyl xanthogen was prepared by the method of Pomianowski and Jeja[13] and was used immediately for the synthesis of If. The THP ethers of Ib-d and compounds Id and Ie were synthesized by reacting the sodium salts of Vb-VIIb, and the sodium salts of diethyl dithiocarbamate and ethyl xanthogen with Ia in DMF at room temperature under nitrogen. The free phenols Ig-i were obtained by mild acid hydrolysis of the corresponding THP ethers in aqueous THF.

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Johns Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727B spectrophotometer. NMR spectra were taken on a Varian Associates model HFT-80 MHz spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on LKB 9000 GC-MS spectrometer at the Gortner Biochemistry Laboratory of the University of Minnesota, St. Paul, MN. Elemental analyses on chemical compounds were performed by Galbraith Laboratories, Inc. (2323 Sycamore Drive, Knoxville, TN 27921), and by M-H-W Laboratories (P. O. Box 15853, Phoenix, AZ 85018).

3-(3,5-Di-t-butyl-4-hydroxybenzyl)-2,4,6-trimethylbenzyl chloride (IV).- To a stirred solution of 168.5 g (1.0 mol) of II in 600 mL dichloromethane at -5° were added dropwise simultaneously solutions of 125 g (0.53 mol) of III in 800 mL dichloromethane over 1 hr. and 80 mL 80% sulfuric acid over 30 min. The purple reaction mixture was stirred at -5° for an additional 1 hr. To this solution were added additional amounts of 125 g (0.53 mol)

of III in 800 mL dichloromethane and 80 mL 80% sulfuric acid. After one additional hr. of stirring, the reaction mixture was poured onto 2L of ice-water mixture. The organic layer was separated and washed three times with water, saturated sodium bicarbonate solution, and again with water. The dichloromethane solution was dried over magnesium sulfate and the solvent removed in vacuo. The crude product, IV, was obtained as a brown oil. Crystallization from 800 ml petroleum ether (60-70°) gave 168 g (43.5%) of IV, mp. 118-120°. Recrystallization from a mixture of diethyl ether/pet. ether (1:10 v/v) gave 140 g (36.2%) pure product, mp. 121-122°. Analytical sample was prepared from preparative LC, mp. 122-123°.

Anal. Calcd. for $C_{25}H_{35}OCl$: C, 77.59; H, 9.12; Cl, 9.16. Found: C, 77.73; H, 9.24; Cl, 9.36.

IR(KBr): 3685-3580 cm^{-1} (-OH); NMR ($CDCl_3$): δ 6.91 (s, 1H), 6.81 (s, 2H), 4.99 (s, 1H, -OH), 4.71 (s, 2H, $ArCH_2Cl$), 3.96 (s, 2H, $ArCH_2Ar$), 2.41 (s, 3H, $ArCH_3$), 2.33 (s, 3H, $ArCH_3$), 2.25 (s, 3H, $ArCH_3$), 1.37 (s, 18H, $C(CH_3)_3$); mass spectrum (70 eV) m/e (rel. intensity): 387 (26.1), 386.1 (100, 388 (32), 352 (3.6).

3,5-Bis(3,5-di-t-butyl-4-hydroxybenzyl)-2,4,6-trimethylbenzyl chloride (Ia).- To a stirred solution of 127 g (0.33 mol) of IV in 600 mL dichloromethane cooled at -5° were added dropwise simultaneously solutions of 38.8 g (0.165 mol) of III in 500 mL dichloromethane over one hr. and 50 mL 80% sulfuric acid over 30 min. The reaction mixture was stirred at -5° for an additional hr. To this solution were added second batches of 38.8 g (0.165 mol) of III in 500 ml dichloromethane and 50 mL 80% sulfuric acid. The mixture was allowed to stand at -5° with stirring for another hr. and was then poured onto 2L of ice-water mixture. The organic layer was washed three times with 1L water, saturated sodium bicarbonate solution, water, and was dried over anhydrous magnesium sulfate. The

dichloromethanewas removed in vacuo. The crude product was crystallized from 800 ml petroleum ether (60-70°) to give 84 g (42.1%) of Ia, mp. 156-160°. Recrystallization from a mixture of diethyl ether/pet. ether (1:10 v/v) gave 72.6 g (36.4%) pure Ia, mp. 159-160°. Analytical sample was prepared from preparative LC, mp. 160-161°.

Anal. Calcd. for $C_{40}H_{57}O_2Cl$: C, 79.37; H, 9.5; Cl, 5.86. Found: C, 79.33; H, 9.39; Cl, 5.80.

IR(KBr): 3685-3580 cm^{-1} (OH); NMR ($CDCl_3$): δ 6.82 (s, 4H, $Ar(\underline{H})_4$, 4.98 (s, 2H, -OH), 4.80 (s, 2H, $ArC\underline{H}_2Cl$), 4.01 (s, 4H, $ArC\underline{H}_2Ar$), 2.40 (s. 6H, $Ar(Cl)(C\underline{H}_3)_2$), 2.18 (s, 3H, $ArC\underline{H}_3$), 1.35 (s, 36H, t-butyl); mass spectrum (70 eV) m/e (rel. intensity): 605.4 (85), 604.5 (100), 606.5 (51), 370.8 (2.0).

General procedure for the synthesis of Ib-f.- To a solution of sodium salt of 0.049 mol of Vb in 100 ml DMF was added dropwise a solution of 25 g (0.041 mol) of Ia in 200 mL DMF over 30 min. The reaction mixture was stirred at R.T. under nitrogen atmosphere for 24 hrs. DMF was removed in vacuo and the crude product was dissolved in dichloromethane. The solution was washed with water, and was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the products were recrystallized from pet. ether and ether mixture.

3,5-Bis(3,5-di-t-butyl-4-hydroxybenzyl)-1-(4-oxytetrahydropyranylphenoxymethyl) mesitylene (Ib).- The sodium salt of 8.87 g (0.049 mol) of Vb was allowed to react with 25 g (0.041 mol) of Ia. The yield of Ib was 23.4 g (74.8%), mp. 178-179° (chloroform/pet ether). Analytical sample was prepared from preparative LC, mp. 179-180°.

Anal. Calcd. for $C_{51}H_{70}O_5$: C, 80.27; H, 9.25. Found: C, 80.36; H, 9.39.

IR: 3680-3580 cm^{-1} (-OH); NMR ($CDCl_3$): δ 6.97 (s, 2H, $OAr(\underline{H}'_2)O$), 6.96

(s, 2H, OAr($\underline{H}''_2$)O), 6.84 (s, 4H, Ar($\underline{H}_2$)((CH_3)$_3$), 5.75 (m. 1H, THP ether), 5.06 (s, 2H, -O$\underline{H}$), 4.95 (s, 2H, (Ar$\underline{CH}_2$O), 4.00 (s, 4H, Ar$\underline{CH}_2$Ar), 2.94 (m, 2H, THP ether), 2.32 (s, 6H, Ar($\underline{CH}_3$)(CH_2OTHP)), 2.20 (s, 3H, Ar$\underline{CH}_3$), 1.88-1.48 (m, 6H, THP), 1.34 (s, 36H, t-butyl); MS (70 eV, m/e (rel. intensity)): 679.0 (4.5), 570.8 (100.0), 110.1 (3.5), 84.3 (1.6).

(Ic).- The sodium salt of 11.62 g of VIb was allowed to react with 25 g of Ia. The yield of Ic was 23.5 g (70.1%), mp. 200-202° (chloroform/pet. ether). Analytical sample was prepared from preparative LC, mp. 204-205°.
Anal. Calcd. for $C_{55}H_{78}O_5$: C, 80.64; H, 9.60. Found: C, 80.93; H, 9.81.
IR(KBr): 3680-3585 cm^{-1} (-OH); NMR ($CDCl_3$): δ 7.10 (s, 1H, Ar($\underline{H}$)), 6.93 (m, broad, 2H, Ar($\underline{H}_2$)), 5.57 (m, 1H, THP ether), 4.95 (2, 2H, -OH), 5.05 (s, 2H, OAr$\underline{CH}_2$O), 4.00 (s, 4H, (Ar$\underline{CH}_2$Ar)$_2$), 3.94 (m, 2H, THP ether), 2.32 (s, 6H, Ar($\underline{CH}_3$)(CH_2OTHP)), 2.20 (s, 3H, Ar$\underline{CH}_3$), 1.88-1.48 (m, 6H, THP), 1.39 (s, 9H, t-butyl), 1.34 (s, 36H, t-butyl); MS (70 eV, m/e (re. intensity)): 735 (17.9), 570.6 (100.0), 166.2 (13.9), 84.1 (7.2).

(Id).- Upon subsequent recrystallizations yielded pure product, 24.6 g (73.2%), mp. 194-195° (chloroform/pet. ether). Analytical sample was prepared from preparative LC, mp. 195-196°.
Anal. Calcd. for $C_{55}H_{78}O_5$: C, 80.64; H, 9.60. Found: C, 80.69; H, 9.73.
IR(KBr): 3680-3585 cm^{-1} (-OH): NMR ($CDCl_3$): δ 6.99-6.96 (m, 3H, Ar($\underline{H}_3$)), 6.83 (s, 4H, Ar($\underline{H}_2$)$_2$), 5.57 (m, 1H, THP), 5.05 (s, 2H, Ar$\underline{CH}_2$OAr), 4.95 (s, 2H, -OH), 4.01 (s, 4H, (Ar$\underline{CH}_2$Ar)$_2$), 3.94 (m, 2H, THP), 2.33 (s, 6H, Ar($\underline{CH}_3$)$_2$), 2.21 (3H, Ar($\underline{CH}_3$)), 1.88-1.48 (m, 6H, THP), 1.34 (s, 36H, t-butyl), 1.28 (s, 9H, t-butyl); MS (70 eV, m/e (rel. intensity)): 735 (1.5), 570.6 (100.0), 166.4 (1.9), 84.0 (4.4).

(Ie).- Subsequent recrystallizations yielded pure material, 19.0 g (80.1%), mp. 129-131° (chloroform/pet. ether). Analytical sample was prepared by

preparative LC, mp. 130-132°.

Anal. Calcd. for $C_{45}H_{67}O_2NS_2$: C, 75.26; H, 9.40; S, 8.93. Found: C, 75.22; H, 9.65; S, 8.68.

IR(KBr): 3685-3580 (-OH), 3500-3120 (-OH), 2948-2922 (CH_2S), 2877-2846 (CH_2S), 2800 ($N(CH_3)_2$), 1420 (C=S), 1250-1200 (RC=S(SX)), 1140-1110 (RC(=S)(SX)), 1070-1020 (RC(=S)(SX)), cm^{-1}; NMR ($CDCl_3$): δ 6.80 (s, 4H, $Ar(\underline{H}_2)_2$), 4.95 (s, 2H, -O<u>H</u>), 4.54 (s, 2H, $ArC\underline{H}_2S$), 4.69-3.88 (m, very broad, 4H, $N(C\underline{H}_2)$), 4.00 (s, 4H, $(ArC\underline{H}_2Ar)_2$), 2.36 (s, 6H, $Ar(CH_3)_2$) 2.14 (3H, $ArC\underline{H}_3$), 1.53-1.19 (m, broad, 6H, $N(CH_2C\underline{H}_3)$), 1.34 (s, 36H, t-butyl); MS (70 eV, m/e (rel. intensity): 718.16 (37.8), 570.0 (100.0), 148.1 (2.3).

(If): Pure products was obtained from isolation of the major product from preparative LC, 12.8 g (56.0%), mp. 155-158°. Analytical sample was prepared from preparative TLC GF, mp. 159-160°.

Anal. Calcd. for $C_{43}H_{62}O_3S_2$: C, 74.73; H, 9.04; S, 9.28. Found: c, 75.10; H, 9.12; S, 9.86.

IR(KBr): 3680-3600 (-OH), 2948-2922 (CH_2S), 2877-2846 (CH_2S), 1420 (C=S), 1250-1200 (RC=S(SX)), 1140-1110 (RC(=S)(SX)), 1070-1020 (RC(=S)-(SX)), cm^{-1}; NMR ($CDCl_3$): δ 6.79 (s, 4H, $Ar(\underline{H}_2)_2$), 4.96 (s, 2H, -O<u>H</u>), 4.73-4.65 (q, 2H, J=15Hz; $C\underline{H}_2CH_3$), 4.49 (s, 2H, $ArC\underline{H}_2S$), 3.98 (s, 4H, $(ArC\underline{H}_2Ar)_2$), 2.33 (s, 6H, $Ar(C\underline{H}_3)_2$), 2.15 (s, 3H, $ArC\underline{H}_3$), 1.53-1.26 (t to m, 3H, J=15Hz; $C\underline{H}_3CH_2$), 1.34 (s, 36H, t-butyl); mass spectrum (70 eV) m/e (rel. intensity): 691.7 (2.9), 570 (100), 105.1 (0.9).

Acid Hydrolysis of Ib-d.- To a stirred solution of 20.0 g of the THP ether in 200 mL THF under nitrogen was added dropwise 15 mL 6N HCl over a period of 24 hrs. The reaction mixture was neutralized with NaOH pellets. The ppt. was removed by filtration. The solvent was removed in vacuo. The crude product was crystallized from ether and pet. ether mixture.

(3,5-Bis(3,5-di-t-butyl-4-hydroxybenzyl)-1-(4-hydroxyphenoxymethyl) mesitylene (Ig).- Mild acid hydrolysis of Ib gave Ig, 15.06 g (85.3%), mp. 180-181° (chloroform/pet ether). Analytical sample was prepared from preparative LC, mp. 183-184°.

Anal. Calcd. for $C_{46}H_{62}O_4$: C, 81.37; H, 9.20. Found: C, 81.07, H, 9.21. IR(KBr): 3685-3585 (-OH), 3590-3010 cm^{-1} (-OH); NMR ($CDCl_3$): 7.19-6.88 (m, 4H, OAr($\underline{H}_4$)O), 6.84 (s, 4H, Ar($\underline{H}_2$)$(CH_3)_3$), 5.04 (s, 2H, -O$\underline{H}$), 4.95 (s, 2H, Ar$\underline{CH}_2$OArOH), 4.48 (s, 1H, -O$\underline{H}$), 4.00 (s, 4H, (Ar$\underline{CH}_2$Ar)$_2$), 2.32 (s, 6H, Ar($\underline{CH}_3$)$_2$OAr-OH), 2.20 (s, 3H, Ar-$\underline{CH}_3$)), 1.34 (s, 36H, t-butyl); MS (70 eV) m/e (rel. intensity): 678.0 (0.6), 570.0 (100), 110 (1.8).

2,4,6-Trimethyl-3,5-bis(3',5'-di-t-butyl-4'-hydroxybenzyl)-1-(3"-t-butyl-4"-hydroxyphenoxymethyl)benzene (Ih).- Mild hydrolysis of Ic gave Ih, 14.1 g (80.2%), mp. 124-125° (chloroform/pet ether). Analytical sample was prepared by preparative LC, mp. 125-126°.

Anal. Calcd. for $C_{50}H_{70}O_4$: C, 8170; H, 9.60. Found: C, 81.43; H, 9.88. IR(KBr): 3686-3585 (-OH), 3590-3200 cm^{-1} (-OH); NMR ($CDCl_3$): 6.96-6.64 (m, 3H, -ARC$\underline{H}_3$), 6.86 (s, 4H, Ar($\underline{H}_2$)$_2$, 4.97 (s, 2H, -O$\underline{H}$), 5.05 (s, 2H, Ar$\underline{CH}_2$OAr), 4.58 (s, 1H, -O$\underline{H}$), 4.03 (s, 4H, Ar-$\underline{CH}_2$-Ar), 2.35 (s, 6H, Ar($\underline{CH}_3$)$_3$), 2.23 (s, 3H, Ar($\underline{CH}_3$)), 1.40 (s, 9H, t-butyl), 1.36 (s, 36H, t-butyl); MS (70 eV) m/e (rel. intensity): 735 (13.4), 570 (100), 166 (13.0)

2,4,6-Trimethyl-3,5-bis(3',5'-di-t-butyl-4'-hydroxybenzyl)-1-(2"-t-butyl-4"-hydroxyphenoxymethyl)benzene (Ii).- Mild hydrolysis of Id gave Ii, 13.8 g (78.6%), mp. 123-124° (chloroform/pet ether).

Anal. Calcd. for $C_{50}H_{70}O_4$: C, 81.70; H, 9.60. Found: C, 81.70; H, 9.78. IR(KBr): 3680-3585 (-OH), 3590-3200 cm^{-1} (-OH); NMR ($CDCl_3$): 6.92-6.84 (m, 3H, Ar($\underline{H}_3$)), 6.87 (s, 4H, Ar($\underline{H}_2$)), 5.05 (s, 2H, Ar$\underline{CH}_2$OAr), 4.99 (s,

2H, -OH), 4.57 (s, 1H, -OH), 4.05 (s, 4H, $ArCH_2Ar$), 2.37 (s, 6H, $Ar(CH_3)_2$), 2.17 (s, 3H, $Ar(CH_3)$), 1.37 (s, 36H, t-butyl), 1.30 (s, 9H, t-butyl); MS (70 eV) m/e (rel. intesnsity): 735 (6.8), 570 (100), 166 (16.7).

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